Remarks

Claims 1 is amended herein, claims 2-8 are cancelled, and claims 9-15 are new. Applicants reserve the right to pursue the cancelled subject matter in one or more divisional applications. Support for amended claim 1 and new claims 9-15 can be found throughout the specification and in claims 1-8 as originally filed. No new matter is added.

Rejection under 35 U.S.C. § 103(a):

The Examiner has rejected claim 1 under 35 U.S.C. § 103(a) as being unpatentable over Kreidstein et al., Canadian J. Phys. And Pharm., 70:1208-1216 (1992) or Davies et al., Ann. Plastic Surgery, 40:630-636 (1998) (claim 1) in view of Cederqvist et al., Biochem. Pharm., 47:1047-1053 (1994). Complete copies of these references are enclosed for the Examiner's convenience.

Amended claim 1 recites a method of preventing necrosis in a pedicle flap by topically applying an effective amount of a vasodilator composition comprising an NO donor that causes formation of nitrosothiol in tissue. New claims 9-15 directly or indirectly depend from claim 1. Applicants traverse the rejection with respect to these claims as amended and added herein.

The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. *See In re Dow Chemical Co.*, 837 F.2d 469 (Fed. Cir. 1988). It is also well recognized that a prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *See W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983). Further, it is improper to combine references where the references teach away from their combination. *See In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983).

Moreover, the mere fact that these references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one ordinary skill in the art. *See* MPEP §2143.01, citing *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385, 1396 (2007). Furthermore, a statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" because the references relied upon teach that all

aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *See* MPEP §2143.01, citing *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (emphasis original).

Applicants submit there is no objective reason provided by either Kreidstein or Davies, in combination with Cederqvist, that would provide the skilled artisan with a reasonable expectation that the claimed class of NO donors (i.e., NO donors which form nitrosothiol in tissue) would be effective to prevent flap necrosis.

Davies and Kreidstein merely describe the use of nitroglycerin (along with other compounds) to induce vasodilation. Neither, Davies or Kreidstein describe the use of an NO donor that causes nitrosothiol formation in tissue for preventing skin flap necrosis during surgery, as required by the instant claims, as nitroglycerin is not a member of this specific class of NO donors, since it is not capable of directly forming nitrosothiol. That is, nitroglycerin, while considered an NO donor, has a completely different biochemical and physiological profile than NO donors which form nitrosothiols. Cederqvist fails to cure the deficiencies in the teachings of Davies and Kreidstein. Cederqvist merely describes specific types of organic nitrites, including nitroglycerin, that can serve as NO donors.

There is no evidence that the skilled artisan, reading the combination of these references, would swap any one NO donor for any other NO donor (as asserted by the Examiner) to reach the present invention with predictable results. In fact, Davies and Kreidstein both teach that a significant amount of unpredictability exists regarding the efficacy of different types of vasodilator compositions, including nitrovasodilators, in mediating skin flap survival.

Davies describes the evaluation of three different types of vasodilators, phenoxybenzamine (an alpha adrenergic antagonist), nifedipine (a calcium channel blocking agent), and nitroglycerin (a nitrovasodilator), for their ability to improve random-pattern skin flap ischemia caused by mainstream exposure to cigarette smoke. As described in Davies, variable results were achieved with the three different types of vasodilators. More specifically, one of the vasodilators, phenoxybenzamine, failed to improve skin flap viability; and, although, the calcium channel blocking agent and nitroglycerin each improved viability, Davies states that "the cause for this phenomenon is unknown".[1] That is, there is nothing to lead the skilled artisan

[1] *See* Davies at page 635, first column, lines 41-47.

to select any one, alpha adrenergic antagonist, calcium channel blocking agent or nitrovasodilator, over any other, that would have an expected vasodilation effect.

Likewise, Kreidstein teaches the use of nitroglycerin to study endothelium independent vasodilation in human skin flaps using an isolated, perfused skin flap model, and suggests that nitrovasodilators, such as nitroglycerin, may be used to prevent skin flap ischemia. However, Kreidstein teaches away from the Examiner's assertion that any NO donor would be interchangeable for any other as the Authors state that the efficacy for nitroglycerin intervention is unclear, citing evidence where topical nitroglycerin was both effective and ineffective in augmenting skin flap viability.[2] Kreidstein additionally warns that "further studies on the role of NO in the pathophysiology and pharmacology of the skin flap are required".[3]

Based on the foregoing, the skilled artisan reading the combination of Davies, Kreidstein and Cederqvist as a whole, as required, would not exchange nitroglycerin, as taught by these references, for an NO donor that generates nitrosothiol formation in tissue to reach the present invention with predictable results.

Additionally, a determination of whether the claimed subject matter as a whole would have been obvious at the time the invention was made also involves factual findings with respect to secondary considerations, including failure of others and superior/unexpected results. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

The present invention provides superior properties not taught or suggested by the combination of Davies, Kreidstein and Cederqvist. As evidenced by the variable and inconsistent results described in Davies and Kreidstein, not all vasodilating compounds were capable of inducing vasodilation to mediate skin flap survival, and nitroglycerin was unable to assert its effects on all types of skin flaps (*e.g.*, random-pattern, axial-pattern and free vascularized flaps) and across all species.

More importantly, the biochemical and physiological profile of nitroglycerin renders this compound ineffective at preventing necrosis in a pedicle flap, or in any microvascular surgery, when compared to the claimed NO donors which directly generate nitrosothiols in the tissue.

The data described in Kreidstein and Davies demonstrating any effectiveness of nitroglycerin in preventing flap necrosis is mischaracterized and inapplicable to the instant

[2] *See* Kreidstein at page 1215, first column, lines 9-15.
[3] *See* Kreidstein at page 1215, first column, lines 16-18.

invention. That is, the isolated perfusion and ischemia models utilized by Kreidstein and Davies, respectively, are not physiologically relevant models for studying the prevention of skin flap necrosis during surgery or under physiological conditions because these models lack the essential components for skin flap survival: blood vasculature and red blood cells.

It is well known in the art that nitroglycerin is an inefficient NO donor because it first requires biotransformation by a mitochondrial enzyme in order to release NO.[4,5] This required mitochondrial enzyme is not present in blood, as red blood cells do not contain mitochondria. Even if it the enzyme were present, the skilled artisan would be readily aware that nitric oxide is inactivated in blood.[6,7] Thus, a compound that merely generates NO, such as nitroglycerin, would not be effective to prevent skin flap necrosis in a surgical setting where the presence of blood flow in the skin flap is essential to flap survival.

In contrast, nitrosothiol generating compounds, such as those claims, are much more effective than nitroglycerin, or other types of NO donors, in mediating skin flap necrosis in a physiological environment. Specifically, the *direct* formation of nitrosothiol by these compounds prevents their immediate inactivation by blood and creates reservoirs of NO activity in the tissue, thereby providing a longer biological activity profile than other types of NO donors. Additionally, nitrosothiol generating compounds, as claimed, are more effective than compounds such at nitroglycerin, as these nitrosothiol generating compounds dilate both arteries and veins, whereas most other NO donor compounds, such as nitroglycerin, only have venous activity.

These unexpected and superior properties of the claimed nitrosothiol forming NO donors is not taught or suggested by the combination of Davies, Kreidstein and Cederqvist.

Applicants request reconsideration and withdrawal of the present rejections.

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[4] *See* Chen et al., PNAS, 99(12): 8306-8311 (2002). A complete copy of this reference is submitted in the accompanying Supplemental Information Disclosure Statement for consideration by the Examiner.
[5] *See* Chen et al., PNAS, 102(34): 12159-12164 (2005). A complete copy of this reference is submitted in the accompanying Supplemental Information Disclosure Statement for consideration by the Examiner.
[6] *See e.g.*, Casadevall et al., Gastroenterology, 110(4):1156-1165 (1996). A complete copy of this reference is submitted in the accompanying Supplemental Information Disclosure Statement for consideration by the Examiner.
[7] *See e.g.*, U.S. Patent No. 6,455,676.

Conclusion

Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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